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INCIDENCE ON COST AND DURATION OF THERAPY FOR POTENTIAL INFECTIONS IN POST-OPERATIVE TRAUMATIC WOUNDS WITH PROSTHETIC DEVICES, PREVIOUSLY TREATED AND UNTREATED WITH ANTIBACTERIAL GELS AT SAN GIULIANO HOSPITAL ASL NAPLES 2 NORTH

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Abstract

Introduction

Bacterial infections associated with implanted biomaterials represent the most significant complication in orthopedics, constituting the leading cause of failure in primary hip and knee prostheses. Prevention of infections associated with implanted biomaterials should simultaneously focus on at least two objectives: inhibition of biofilm formation and minimization of suppression of the local immune response. Some technologies proposed for this purpose in clinical practice have already demonstrated strong evidence of antibacterial efficacy, safety, and resistance. The time is ripe for further development and experimentation of these technologies in a clinical setting.

Materials and Methods

The study involved observing wounds in the 6 months following treatments (Follow Up). The aim was to evaluate the cost-benefit aspects in patients treated with defensive antibacterial gels during orthopedic interventions for prostheses and/or synthesis at the San Giuliano Hospital, ASL Napoli 2 North. The goal was to assess the effectiveness of the treatment applied to patients undergoing orthopedic interventions for prostheses and/or orthopedic synthesis. The wounds of treated and untreated patients were compared six months post-surgery, along with the costs incurred by the National Health Service (NHS) and the respective benefits obtained for treated and untreated patients. The observational and retrospective study spanned six months and involved a cohort of 60 patients from the orthopedic department and outpatient clinic of San Giuliano Hospital, ASL Napoli 2, undergoing post-traumatic interventions. The cohort was divided into two groups: Group A (gA) included 30 operated patients whose wounds or devices used were treated with decontamination gels to prevent infections, while Group B (gB) consisted of 30 patients operated on but not treated with any such device. The study involved a six-month observation of the two groups, evaluating the possible occurrence of infections, their duration (until complete healing, including any complications), and the average cost of therapy required for treatment (monitoring the use of drugs, supplies, and devices). A scale of values was then set up based on the average cost incurred and the average duration of treatment for each of the 4 levels of the scale.

Results

At the end of the period, 30 patients from Group A and 30 from Group B were observed. Within Group A, 2 patients reported infections, placing them in the first two levels of the scale. In Group B, 8 patients required treatment for infections, placing them at different levels of the scale based on the treatment received and its associated cost. The economic impact is high and varies depending on the breadth of usage indications, such as applying the device alone or as a carrier in association with antibiotics for all subjects undergoing primary and revision arthroplasty or osteosynthesis surgical procedures, or only for a fraction of them (e.g., patients at risk of infections, subjects undergoing prosthesis re-implantation, osteosynthesis of traumatic exposed fractures, etc.).

Conclusions

Managing an infection that develops after an orthopedic intervention for prostheses and/or synthesis leads patients to seek long-term medical check-ups and specialized nursing assistance. The total costs for treating the 10 infected patients show that the overall expenditure for the 8 in Group B is much higher than that for the total of 2 in Group A, both because of the fivefold increase in numbers and the milder and more treatable nature of infections in the two patients in Group A. Even when considering the costs related to the use of antibacterial gels on wounds or prosthetic devices/osteosynthesis, the economic savings are significant considering the cost of pharmacological treatments for infections and their potential complications.

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Introduction

Bacterial infections associated with implanted biomaterials represent the most significant complication in orthopedics and constitute the primary reason for the failure of primary hip and knee prostheses. The incidence varies between 0.5% and 4% and can occur even under excellent aseptic conditions with the correct surgical procedure and adequate systemic antibiotic prophylaxis. In traumatology, infectious complications after osteosynthesis occur at a rate ranging from 0.5% to 25% of cases, depending on the type and site of the fracture, the level of bone exposure, and the degree of soft tissue contusion.

The pathogenesis of infections from implants or internal fixation devices is generally characterized by the bacterial ability to colonize the surfaces of implant devices and different biomaterials, forming a biofilm. When the implant or the surrounding tissue is contaminated, a "race to the surface" occurs between host cells and bacteria. Compared to immune system cells, bacteria have the advantage of faster reproductive processes and extreme adaptability to the environment; bacterial colonization can form a protective biofilm just a few hours after the initial adhesion to any implanted device.

Preventing infections associated with implanted biomaterials must simultaneously focus on at least two objectives: inhibiting biofilm formation and minimizing the suppression of the local immune response. A broad spectrum of substances and technological approaches has been proposed for treating surfaces in orthopedic surgery and tested for antibacterial characteristics. A change in the chemistry and/or structure of the prosthetic surface can be achieved either chemically or physically by altering the surface layer of the existing biomaterial (e.g., through oxidation or mechanical modifications such as roughening/polishing/texturing). Another method involves overlaying the existing surface with a new thin layer of material with a different composition (e.g., hydroxyapatite coating, antibiotics covalently bound to a substrate, fixation of other antimicrobial compounds).

In terms of durability, a distinction can be made between degradable and non-degradable biomaterials. Table 1 provides examples of proposed anti-infective strategies for the antibacterial treatment of implantable surfaces used in orthopedic surgery (from: Gallo J, Holinka M, Moucha CS. Antibacterial Surface Treatment for Orthopaedic Implants. Int. J. Mol.).

To provide a more in-depth perspective on the topic, a narrative review (Gallo et al., 2014) was selected on innovative strategies and techniques proposed for the antibacterial treatment of implantable surfaces used in orthopedic surgery. The study presents current knowledge on antimicrobial surface treatments aimed at preventing prosthetic infections.

STRATEGY	FEATURES	EXAMPLES
Prevention in adhesion and adsorption		Anti-adhesive polymers
		Albumin
		Super-hydrophobic surface
		Hydrogels
Methods to kill bacteria	Inorganic	Silver nanoparticels
		Titanium dioxide
		Selenium Ion
		Copper ion
		Zinc ion
	Organic	Coated or covalently linked antibiotics
		Chitosan derivatives
		Cytokines
		Enzymes
	Other	Non-antibiotic bacterial substances
	Combined	Multilayer coating
		Sinergy material intensification
		Positively charged polymers
Multi-Functional and smart coating	Passive	Nanostructured "smart" material
Multi-Functional and smart coating	Active	Concept: sensors conjoined to nanoconainers
Alternative approach		Lytic bacteriophages

Table 1 *Types of Antibacterial Devices in Use*

The authors conclude that research in the field of superficial antibacterial treatment of orthopedic implants has demonstrated in vitro and in vivo efficacy of various potentially promising technologies. Some interfere with bacterial adhesion and the initial stages of biofilm formation, while others exhibit direct antibacterial properties. Issues related to the mechanical properties of such technologies and potential harmful effects, such as toxicity and interference with osteointegration, require further investigation.

Some of the proposed technologies have already shown strong evidence of antibacterial efficacy, safety, and resistance. The time is ripe for further development and experimentation of these technologies in a clinical setting. In selected studies evaluating individual components of the gel (hyaluronic acid and polylactic acid), the individual

components in association with antibiotics were tested in vitro.

In Aviv's in vitro study (2007), polylactic acid, in hydrogel associated with gentamicin, released antibiotic concentrations effective over time against bacterial species known to be involved in orthopedic infections. In HU's in vitro study (2010), titanium (Ti) surfaces were functionalized with carboxymethyl-chitosan (CMCS) or hyaluronic acid-catechol (HAC). The vascular endothelial growth factor (VEGF) was then conjugated to the surfaces of the grafted polysaccharides. Antibacterial testing with Staphylococcus aureus (S. aureus) showed that VEGF-modified polysaccharide substrates significantly reduce bacterial adhesion.

A rapidly absorbable and biocompatible hyaluronic acid-derived biopolymer hydrogel has recently been patented. The multinational project, "A Novel Approach to Implant-Related Infections in Orthopedics and Trauma Surgery," developed and validated an absorbable and antibacterial coating to prevent implant-related infections during orthopedic and trauma surgery. The hydrogel is designed for intraoperative antibiotic loading, preventing bacterial colonization and biofilm formation while minimizing the risk of emerging drug-resistant bacterial strains. Project members evaluated the safety, costs, effectiveness, ease of use, duration, and sterilization of the hydrogel. Two successful clinical trials related to hip and knee arthroplasty and traumatology were completed during the project's final phase. Researchers confirmed the quality, durability, and safety of the products and validated sterilization through beta irradiation. In vitro tests were conducted to assess the effectiveness of products pre-loaded with antibacterial agents. Tested antibacterial agents include vancomycin, gentamicin, tobramycin, amikacin, and N-acetylcysteine (NAC). Good antibiofilm activity against pathogens such as Staphylococcus aureus and Staphylococcus epidermidis was observed without any cytotoxicity.

Project prototypes demonstrated promising results in terms of graft adherence, specifically during human trials with deceased subjects' femurs or in vivo studies on rabbits. In addition to biocompatibility, successful product preparation and application procedures were designed and tested. Clinical studies (randomized, single-blind, control group, multicenter, international) related to traumatology and arthroplasty, along with subsequent 12-month monitoring, have been concluded. Results showed a statistically significant difference between the antibacterial gel product group and the control group. Effectiveness: No infections were reported in the I.D.A.C. product-treated group, while 7.5% of the control group developed an infection (p = 0.0023). Regarding safety, no adverse events related to the product occurred.

Materials and Methods

The study was conducted by observing wounds in the 6 months following the treatments (Follow Up). The purpose of the work was to evaluate the cost and benefit aspects in patients treated with defensive antibacterial gels during orthopedic interventions for prostheses and/or synthesis at San Giuliano Hospital, ASL Napoli 2 North. The goal was to assess the effectiveness of the treatment applied to patients undergoing orthopedic interventions for prostheses and/or orthopedic synthesis at San Giuliano Hospital, ASL Napoli 2 North.

The states of the wounds at 6 months post-orthopedic surgery were compared between treated and untreated patients, along with the costs incurred by the National Health Service (SSN) and the respective benefits obtained for the treated and untreated patients.

The observational and retrospective study spanned 6 months and involved a cohort of 60 patients from the orthopedic department and outpatient clinic of San Giuliano Hospital, ASL Napoli 2, who underwent post-traumatic interventions. The cohort was divided into 2 groups:

Group	Operated	Treatted	N° of Patient	Osteosynthesis	Prosthesis
Group A (gA)	YES	YES	30	21	9
Group B (gB)	YES	NO	30	23	7

Tab 2 Group Division of Operated Patients Constituting the Study Cohort Based on the Received Treatment with Antibacterial Gel.

In Group A (gA), 30 operated patients were included, whose wounds and/or devices were treated with gels aimed at their decontamination to prevent infections. In Group B (gB), 30 operated patients did not receive any treatment with a device for this purpose. The study involved a six-month observation of both groups, evaluating the potential occurrence of infections, their duration (until complete healing, including any complications), and the average cost of the therapy necessary for the treatment. This assessment included monitoring the usage of medications, supplies, and devices. Additionally, a scale of values was set up:

LEVEL	COSTO MEDIO	AVERAGE TREATMENT DURATION
Level 1 (L1)	< 400 €	< 30 days
Level 2 (L2)	401<€>1000	60<days>120
Level 3 (L3)	1001<€ >2000	>90 days
Level 4 (L4)	> 2000 €	≥ 120 days

Tab 3 Scale of Values for the Occurrence of Possible Infections Observed in the 6-Month Follow-Up, with Average Duration and Average Therapy Cost Variables:

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1. At Level 1 (L1), all patients in the cohort whose average therapy cost was less than €400 and with an average treatment duration of less than one month were placed.
2. At Level 2 (L2), all those for whom the therapy cost was between €401 and €1000 and the treatment duration was between 2 and 4 months were placed.
3. At Level 3 (L3), those with a therapy cost between €1001 and €2000 and healing at 3 months were placed.
4. At Level 4 (L4), the remaining patients with a therapy cost exceeding €2000 and a treatment duration of ≥4 months were placed.

All patients in the individual groups were numbered with Roman numerals in ascending order, starting with those in group A (gA) and followed by those in group B (gB).

Results

At the end of the 6-month observation period, it was possible to verify that: • In gA, out of the 30 affiliated patients, one patient reported infections, placing them at Level 1 (L1) on the scale, and another patient was placed in Level 2 (L2).

Graph 1 *Distribution of patients in group A (gA) in relation to the scale of values.*

The patient placed at Level 1 (L1), approximately 28 years old, underwent osteosynthesis surgery and had to undergo a 10-day intramuscular cephalosporin treatment with cefazolin. Additionally, they changed dressings daily, using wound healing and antiseptic agents, disinfecting with iodopovidone and water.

As for the patient assigned to Level 2 (L2), operated for joint prosthesis, vancomycin was administered in the hospital for 7 days, and intramuscular cephalosporin was continued at home for 12 days. Due to a complication arising from the treatment of early pressure ulcers with silver ion spray, related to his not very young age (75 years), he also used dressings to promote healing at average intervals of 24/36 hours, disinfecting with iodopovidone and water.

gA	Patient N° id.	Average Cost	Average Treatment Duration	Osteosynthesis	Prosthesis
Level 1 (L1)	N° I	129 €	14 days	YES	
Level 2 (L2)	N° II	535 €	67 days		YES

Tab 4 *Specification of gA:*

• Out of the 30 affiliated patients in gB, 8 patients required treatment for occurring infections, and within this context, their placement on the scale of values is as follows: 4 patients at Level 1 (L1), 1 patient at Level 2 (L2), 1 patient at Level 3 (L3), and 1 patient at Level 4 (L4).

Graph 2 *Distribution of gB patients in relation to the scale of values.*

Among the patients operated but not treated with antibacterial gels, the costs related to treatments are higher, the occurrence of infection is more frequent, and their severity is generally more significant and challenging. Patient III, 19 years old, operated for osteosynthesis, was placed in L1 due to the onset of a mild infection treated with intramuscular cephalosporins and dressings with disinfection. Patients IV and V, on the other hand, underwent prosthetic interventions, and the infections in these cases were slightly more significant, requiring initial treatment with intravenous vancomycin and later, after discharge, with intramuscular cephalosporins. Patient VI experienced slower healing due to complications influenced by being type II diabetic. We have two patients placed in L2, one operated for osteosynthesis (Patient VII), the other (Patient VIII) for a prosthesis treated initially with linezolid, later with vancomycin, and at home with intramuscular cephalosporins and advanced dressings. In particular, Patient VIII received bi-weekly negative pressure wound treatments.

In the last two cases, for patients IX and X, meropenem had to be resorted to during hospitalization after linezolid and vancomycin did not achieve the expected outcomes. They also faced the treatment of pressure ulcers with soaked dressings and silver spray, eventually receiving intramuscular antibiotic treatment at home while undergoing continuous cleaning sessions with specific irrigation solutions and negative pressure treatment, including advanced dressings, until complete healing.

gB	Patient N° id.	Average Cost	Average Treatment Duration	Osteosynthesis	Prosthesis
Level1 (L1)	N° III	230 €	18 days	YES	
Level1 (L1)	N° IV	398 €	22 days		YES
Level 1 (L1)	N° V	412 €	25 days		YES
Level 1 (L1)	N° VI	524 €	28 days	YES	
Level 2 (L2)	N° VII	857 €	73 days	YES	
Livello 2 (L2)	N° VIII	924 €	86 days		YES
Level 3 (L3)	N° IX	2350 €	94 days	YES	
Level 4 (L4)	N° X	3783 €	131 days	YES	

Tab 5 Specification of gB

The economic impact could presumably be high and variable depending on the scope of usage indications (e.g., applying the device alone or as a carrier in conjunction with antibiotics in all subjects undergoing primary and revision joint arthroplasty surgeries, or osteosynthesis of fractures, or only in a subset of them, e.g., selected patients at risk of infections, subjects undergoing prosthesis replacements, osteosynthesis of traumatic exposed fractures, etc.).

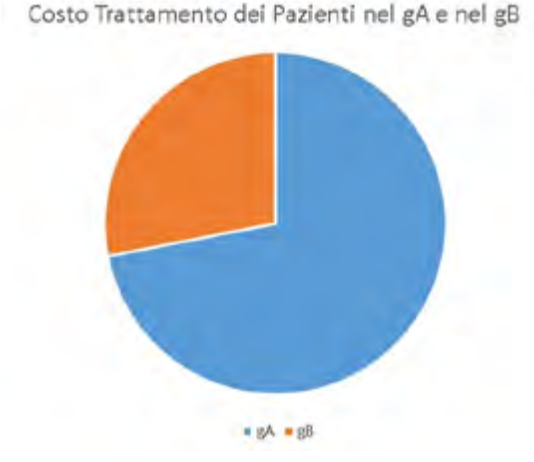
Conclusions

The management of an infection that develops after orthopedic surgery involving prosthetics and/or synthesis is what leads the patient to seek and rely on long-term medical check-ups and specialized nursing care. For the management of infected wounds resulting from orthopedic interventions, it adds an average cost burden to the National Health Service (SSN) of around 800 million euros. If a hip operation costs an average of 9 thousand euros, in the case of serious infections, the final cost figure can rise to a much higher amount, for example:

Type of hip replacement surgery	Cost in euro
15 days of acute hospitalization	9100,00 €
5 consultations for the injury	451.85 €
3 hematology consultations	271.11 €
7 infectious disease consultations	632.59 €
Clinical laboratory monitoring	134,13 €
Antibiotic therapy	3936,66 €
TOTAL COSTS	14.526,34 €

Table 6 Costs for the treatment of a level 3 infected orthopedic wound

The total costs for the care of the 10 infected patients highlight that the overall expenditure for the 8 in group B (7051 euros) is much higher than that of the total for the 2 in group A (664 euros), both because of five times more in terms of numbers, demonstrating how the treatment with antibacterial gel reduces the occurrence of infections. Additionally, the infections that occurred in the case of the 2 patients in group A are much milder and more treatable.



Graph 3 Cost of the treatment of infections in the two groups

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Although considering the costs related to the use of antibacterial gel (approximately 590 euros per kit) on wounds and/or prosthetic devices/for osteosynthesis, the economic savings are still significant considering the cost of pharmacological treatments for infections and those for their potential complications.

Group	Treatment Expense	T.E.+ Antibacterial Gel
gA	664 €	(590€x2)+664 €=1884 €
gB	7051 €	7051 €
Totali	-6387 €	5167 €

Table 7: Pharmacological treatment costs + cost of disinfectant gel device

Despite some recommendations being identified for the better management of skin wounds, to date, there is no specific therapy for the treatment of such injuries. Well-designed clinical studies on sufficiently large samples are very rare, and most treatments are used routinely, even without reliable evidence of their effectiveness. To date, the Italian National Institute of Health has not published anything in this regard, also because international guidelines, before being used in our clinical practice, should be adopted through a specific development process. On average, specialized centers with high patient influx and large implant volumes guarantee:

- Cleanliness of the environment;
- Speed of the intervention;
- Use of antimicrobial gel before wound closure;
- Management of postoperative dressings by experienced personnel. This attention, this patient care, tends to be higher in high-volume centers compared to low-volume ones. In the international literature, it is noted that low-volume prosthetic centers in peripheral areas, or those with relatively low prosthetic surgery numbers, tend to develop more complications, including infections, compared to high-volume prosthetic surgery hospitals.

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